possession of the claimed inventions at the time the application was filed. Applicants have cancelled all pending claims and have added new claims 68-82, each of which is discussed further below.NO new matter has been added.

Each of the new claims is sufficiently supported by the specification. Applicants contend that it is established law that limitations appearing in claims need not be literally recited in the specification. The issue is not whether words used in the claims are present in the specification but, rather whether the concept expressed by the words is present. *In re Anderson*, 176 U.S.P.Q. 331 (C.C.P.A. 1973).

Support for new claim 68 is found generally throughout the specification. In particular, Applicants teach at, for example, page 7, line 25 to page 8, line 19 of the specification, that the present invention is directed, in part, to "systems" for implementing the methods of the invention, *i.e.*, an integrated system for preparing a set of oligonucleotides targeted to a selected nucleic acid and identifying particular members of the set that possess at least one property. The system comprises several components, which is also shown in Figure 18.

The first component of the system is component that prepares a virtual library of oligonucleotides targeted to the selected nucleic acid and generates synthesis instructions in computer manipulable form for each of the oligonucleotides in the virtual library. Such a component is taught by Applicants at, for example, page 61, line 33 to page 62, line 28 of the specification, whereby Applicants teach a computer network comprising a computer engine, database server and file server. The database server stores all the chemical structures as well as contains data relating to synthesis and reagent files (component 520 of Figure 13), and molecular targets (step 205 of Figure 3). The computer engine runs computational programs such as RNA folding, oligonucleotide walking, and genomic searching, *i.e.*, those programs that are used to generate the virtual library of oligonucleotides. The file server allows raw instrument output storage and sharing of robot instructions. Thus, when taken as a whole, Applicants teach that a combination of these three components of the computer network carry out numerous processes that results in the generation of

the virtual library of oligonucleotides as described in greater detail at, for example, page 14, line 28 to page 39, line 14 of the specification.

The second component of the system is an automated synthesizer that receives synthesis instructions from the computer network and synthesizes a set of real oligonucleotides corresponding to the virtual set of oligonucleotides. Such a component is described in the specification at, for example, page 39, line 14 to page 52, line 18 of the specification. Figures 23 and 24 describe one particular embodiment illustrating an apparatus for synthesizing oligonucleotides. The synthesis instructions received by the automated synthesizer are in computer manipulable form represented by, for example, command files (.cmd), sequence files (.seq), and lookup table files (.tab), which are described in detail at, for example, page 40, line 19 to page 41, line 14 of the specification, as well as in Figure 13. In addition, Example 3 of the specification lists typical command, sequence, and lookup table files for a particular oligonucleotide. The automated synthesizer is shown in Figure 18 to be integrated with the computer network.

The third component of the system is an assay apparatus that accepts the set of real oligonucleotides and performs at least one assay for each of the real oligonucleotides. The assay identifies particular members of the set possessing at least one property, wherein the assay is computer-controlled real-time polymerase chain reaction or computer-controlled enzyme-linked immunosorbent assay, each of which is disclosed at, for example, page 57, line 35 to page 58, line 32 of the specification. Assay apparati for performing hybridization or immunoassay type assays are described throughout the specification. In particular, apparati for performing assays are described at, for example, page 61, line 33 to page 62, line 38 of the specification wherein Applicants teach that some systems include instruments and workstations including, for example, an optical density reader, a combined liquid chromatography and mass spectroscopy instrument, a gel fluorescence and scintillation imaging system, a capillary gel electrophoresis system, and a real-time PCR system. Each of these apparati are integrated with the computer network and automated synthesizer as shown in Figure 18.

Thus, Applicants have taught not only the concept expressed by the words, but have also pointed to particular teachings of each of the elements recited in claim 68. Accordingly, when taken as a whole, Applicants were clearly in possession at the time of filing of an integrated system for preparing a set of oligonucleotides targeted to a selected nucleic acid and identifying particular members of the set that possess at least one property.

As described above, the computer engine, database server, and file server recited in claim 69 is described at, for example, page 61, line 33 to page 62, line 28 of the specification.

Claim 70 is supported in the specification at, for example, page 8, lines 12-16 whereby Applicants teach that selected compounds are synthesized, preferably in a robotic manner and then they are robotically assayed for a desired physical, chemical or biological activity. Applicants also teach at, for example, page 11, lines 25-29 that the oligonucleotides generated by the process of the invention can be assayed robotically using cell lines that are tractable to robotic manipulation such as by growth in 96 well plates. Claim 70 is also supported by the originally filed claims.

Physical, chemical, and biological properties recited in claim 71 are taught throughout the specification. In particular, chemical and physical properties are described at, for example, page 20, lines 16-21 of the specification whereby thermodynamic and kinetic properties such as melting temperatures, association rates, dissociation rates are recited. Biological properties such as modulating the expression of the selected nucleic acid is taught at, for example, page 10, lines 24-27 and page 55, line 13 to page 58, line 32 of the specification.

Applicants teach reducing the members of a virtual library of oligonucleotides by eliminating members based on a set criteria, as recited in claim 72, at, for example, page 22, line 33 to page 24, line 33 of the specification whereby Applicants teach eliminating members of a virtual library based on target accessibility. Thus, from the pool of all possible candidate oligonucleotides, a subset having target accessibility can be selected. Applicants also teach at, for example, page 24, line 34 to page 25, line 34 of the specification, eliminating members of a virtual library based on targeting functional regions (claim 74). Thus, from the pool of all possible candidate oligonucleotides, a subset that targets regions such as the transcription start site, 5' cap, 5'UTR, start

codon, coding region, stop codon, 3'UTR, 5' splice site, 3' splice site, specific exons, specific introns, mRNA stabilization signal, mRNA destabilization signal, poly-adenylation signal, poly-A addition site, poly-A tail, or gene sequence 5' of known pre-mRNA can be selected (claim 75).

Claim 73, which recites that the members of the virtual library of oligonucleotides are reduced by a process of selection based on a uniform distribution of oligonucleotide compounds across the selected nucleic acid is supported in the specification at, for example, page 25, line 35 to page 26, line 22 of the specification,

Claim 76, which recites that selected chemical modifications are applied to the virtual oligonucleotide compounds to generate chemically modified virtual oligonucleotides is supported in the specification at, for example, page 26, line 23 to page 39, line 13, which is replete with chemical modifications to the base, sugar and internucleoside linkage that can be used in the present invention. Such modifications are represented in a sequence file, such as is disclosed in Table 4, at page 75 of the specification.

Applicants teach in, for example, original claim 19, that the selected nucleic acid can be genomic DNA, cDNA, polymerase chain reaction product, expressed sequence tag, mRNA or structural RNA (claim 77).

Claim 78 is supported in the specification at, for instance, Example 1 whereby Applicants teach that human CD40 mRNA was used as a selected nucleic acid.

Applicants teach at, for example, page 61, line 33 to page 62, line 38 of the specification several apparati for performing assays, including, for example, an optical density reader, a combined liquid chromatography and mass spectroscopy instrument, a gel fluorescence and scintillation imaging system, a capillary gel electrophoresis system, and a real-time PCR system. Each of these apparati can also be integrated with the computer network and automated synthesizer as shown in Figure 18. Thus, Applicants' claimed system can have more than one assay apparatus.

Claim 80, which recites that the property is modulating the selected nucleic acid, is supported in the specification at, for example, page 10, lines 24-27 and page 55, line 13 to page 58, line 32 of the specification. Indeed, Applicants teach that protein levels can be determined by

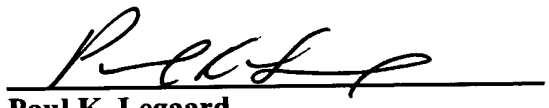
enzyme-linked immunosorbent assay or by fluorescence-activated cell sorting, both of which are easily automated processes.

Claim 81, which recites that the computer network searches at least one database for nucleic acids homologous to the selected nucleic acid, is supported in the specification at, for example, page 62, where, as described above, the computer engine can run genomic searching. Such methodology is described in greater detail at, for example, page 10, line 21 to page 18, line 20 where several databases and computer programs are recited.

Applicants teach that the computer network can also search at least one database for alternative transcripts at, for example, page 15, lines 13-23.

In view of the foregoing arguments, the claimed subject matter is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Applicants submit that the claims presently before the Examiner are in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 57, line 14 of the specification has been amended as follows:

--Target protein levels can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), Enzyme-linked immunosorbent assay (ELISA) or fluorescence-activated cell sorting (FACS). Antibodies directed to a protein encoded by a target nucleic acid can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies, (Aerie Corporation, Birmingham, MI or via the world wide web of the internet at [http://www.]ANTIBODIES-PROBES.com/), or can be prepared via conventional antibody generation methods. Methods for preparation of polyclonal, monospecific ('antipeptide') and monoclonal antisera are taught by, for example, Ausubel *et al.* (*Short Protocols in Molecular Biology*, 2nd Ed., pp. 11-3 to 11-54, Greene Publishing Associates and John Wiley & Sons, New York, 1992).--

In the Claims:

Claims 47, 48, 50, and 52-67 have been cancelled. New claims 68-82 have been added.

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